Original Study

Deep Molecular Response Rate in Chronic Phase Chronic Myeloid Leukemia: Eligibility to Discontinuation Related to Time to Response and Different Frontline TKI in the Experience of the Gimema Labnet CML National Network

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Abstract

Background: In the last decade, TKIs improved the overall survival (OS) of chronic myeloid leukemia (CML) patients who achieved a deep and sustained molecular response (DMR, defined as stable MR4 and MR4.5). Those patients may attempt therapy discontinuation. In our analysis, we report the differences in eligibility criteria due to time of response and different TKI used as frontline treatment analyzed in a large cohort of CP-CML patients. **Methods:** Data were exported by LabNet CML, a network founded by GIMEMA in 2014. The network standardized and harmonized the molecular methodology among 51 laboratories distributed all over Italy for the diagnosis and molecular residual disease (MRD) monitoring. **Results:** Out of 1777 patients analyzed, 774 had all evaluable timepoints (3, 6, and 12 months). At 3 months, 40 patients obtained ≥MR4: of them 14 (3.6%) with imatinib, 8 (5.8%) with dasatinib, and 18 (7.4%) with nilotinib ($P = .093$); at 6 months, 146 patients were in MR4: 42 (11%) with imatinib, 38 (28%) with dasatinib, and 66 (27%) with nilotinib ($P < .001$). At 12 months, 231 patients achieved a DMR: 85 (22%) with imatinib, 55 (40%) with dasatinib and 91 (38%) with nilotinib ($P < .001$). Achieving at least ≥MR2 at 3 months, was predictive of a DMR at any timepoint of observation: with imatinib 67% versus 30% of patients with <MR2, with dasatinib 66% versus 28% of patients with <MR2, and with nilotinib 75% versus 30% of patients with < MR2 ($P < .001$). At the same time point, achieving at least ≥MR3 is even more predictive of a DMR at any timepoint: 89% versus 38% of patients with <MR3 with imatinib ($P < .001$), 84% versus 40% of patients with <MR3 with dasatinib ($P < .001$), and 89% versus 49% of patients with <MR3 with nilotinib ($P < .001$). Of 908 patients who reached a DMR, 461 (51%) lost it: the loss of response after >2 years was significant for patients who at 3 months had ≥MR2 (18% vs. 9.9% of pts with <MR2, $P = .038$).**Conclusion:** In

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conclusion, reaching ≥MR2 and a MR3 at 3 months it seems predictive of a DMR at any time point. Considering the prerequisite for a discontinuation with a sustained DMR only a minority of patients can be eligible for the discontinuation, regardless the frontline treatment received.

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Introduction

Treatment free remission (TFR) has become a novel and significant clinical endpoint in chronic phase chronic myeloid leukaemia patients (CP-CML) who have achieved a sustained and deep molecular response (DMR, i.e. a reduction of 4 or 4.5 logarithms from the baseline molecular burden).[1]

Critical findings on the association of long-term DMR and initial responses were explored at first in the IRIS study.[2] As regards the 2003 report, the importance of a reduction to less than 10% at 3 months and 1% at 6 months[3] was underlined. In the follow-up of the same study in 2010, a landmark analysis of BCR::ABL1 values at 6, 12 and 18 months of imatinib therapy showed that event-free survival (EFS) was inferior for patients with >10% at 6 months and >0.1% at 12 and 18 months.[4] Two different groups then established the value of a ratio < 10% at 3 months for the long-term outcome and the achievement of a DMR.[5,6] A recent analysis of the German CML-Study IV confirmed the optimal response time to achieve 1% BCR::ABL1 at about 12 to 15 months for progression-free survival.[7] A sustained DMR has become the prerequisites for a possible discontinuation and was defined as persistence of the same molecular response (MR4 or MR4.5) at 3 consecutive assessments.[8] In the past it has been demonstrated that achievement of MR3 at 3 months of treatment was associated with stable DMR in the long-term outcome and conversely, a sustained MR4.5 is associated with sustained MR3.[9-12] Most of the published data suggested that a stable DMR reduces the risk of resistance.[9-12] International recommendations provided the evidence that a sustained DMR is required for a possible discontinuation, with almost 3 years of MR4 or 2 years of MR4.5 without fluctuation of molecular residual disease.[1] Indeed, the correlation between level of response and event-free survival (EFS) has been extensively debated.[13] The achievement of MMR was found to correlate with EFS and was used as surrogate endpoint for this type of response in the subsequent clinical trials. But in the previous mentioned IRIS trial, the achievement of an MMR at 12 months did not provide an improved EFS as indeed the achievement of CCyR or a MR2.[2] Therefore, we must differentiate the level of response that we have to reach to put the patients in a safe place for the event of discontinuation due to resistance or progression from that to achieve as criteria of discontinuation. The aim of our study is to report the differences in eligibility criteria due to time of response and different TKIs used as frontline treatment analyzed in a large cohort of CP-CML patients.

Patients and Methods

Data were exported from LabNet CML platform, a network founded by GIMEMA in 2014, with an unconditional grant from Novartis. The LabNet network is a platform that connects Hematology Centers and Molecular Biology Laboratories with the aim of facilitating and standardizing the procedures of the most common laboratory tests for CML. The network standardized and harmonized the molecular methodology among 51 laboratories distributed all over Italy for the diagnosis and molecular residual disease (MRD) monitoring. To participate in the network, laboratories fulfilled quality controls and regularly undergo standardization procedures. The connection between the hematology centers and laboratories is managed by a web-based GDPR compliant platform. The number of reported exams and treated patients, new diagnoses, patients who achieved a DMR were available from each center. Responses were expressed on the International Scale (IS %) and were evaluated according to ELN recommendations every 3 months and at least every 6 months in patients in DMR.

Table 1 Comparison Between Patients Evaluable at Each Time Points and the Remaining Cohort

Characteristic	Overall, N = 1777[a]	<3 Evals, N = 1003	All Evals, N = 774	*P*-Value[b]
Treatment, n (%)				.090
Imatinib	909 (51%)	515 (51%)	394 (51%)	
Dasatinib	351 (20%)	213 (21%)	138 (18%)	
Nilotinib	517 (29%)	275 (27%)	242 (31%)	
Sex, n (%)				.6
Male	1031 (58%)	576 (57%)	455 (59%)	
Female	746 (42%)	427 (43%)	319 (41%)	
Age at diagnosis, Median (IQR)	59 (47, 71)	60 (48, 72)	59 (47, 71)	.3

[a] n (%); Median (IQR).
[b] Pearson's chi-squared test; Wilcoxon rank sum test.

Figure 1 Flowchart of the population analyzed.

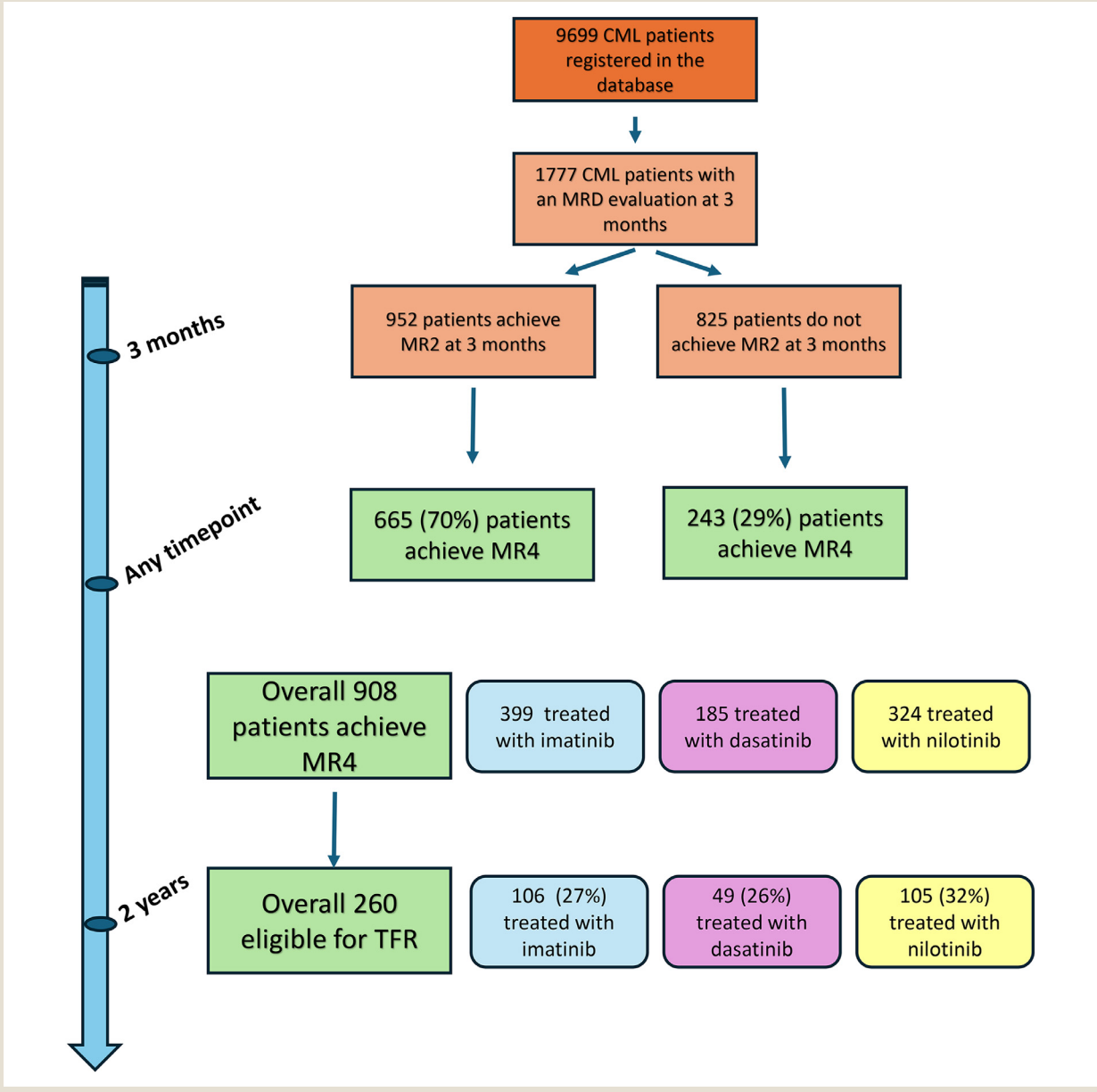

Table 2 Comparison Between TKIs in Terms of Achievement of MR4 at 3, 6, and 12 Months

	3 Mo			6 Mo			12 Mo		
	MR < 4 No = 734	MR ≥ 4 No = 40	*P*-Value	MR < 4 No = 628	MR ≥ 4 No = 146	*P*-Value	MR < 4 No = 543	MR ≥ 4 No = 231	*P*-Value
Treatment no (%)			.093			<.001			<.001
Imatinib	380 (96%)	14 (4%)		352 (89%)	42 (11%)		309 (78%)	85 (22%)	
Dasatinib	130 (94%)	8 (6%)		100 (72%)	38 (28%)		83 (60%)	55 (40%)	
Nilotinib	224 (93%)	18 (7%)		176 (73%)	66 (27%)		151 (62%)	91 (38%)	

Results and Discussion

Data export refers to July 2023: a total of 120,100 evaluable molecular tests were collected and 9699 patients were recorded in the database. Of them 7033 have at least 1 test with a DMR. For this analysis only patients treated in firstline were considered. Patients who switched during the first 24 months were censored.

Out of 1777 patients selected because evaluable since the first evaluation at 3 months, 774 had all evaluable timepoints (3, 6, and 12 months) (Figure 1). A comparison was performed with the remaining patients (Table 1), but no specific differences were detected. At 3 months, 40 patients (5.2%) obtained ≥MR4: of them 14 (4%) with imatinib, 8 (6%) with dasatinib, and 18 (7%) with nilotinib ($P = .093$). At 6 months, 146 patients (18.9%) achieved ≥MR4: 42 (11%) with imatinib, 38 (28%) with dasatinib, and 66 (27%) with nilotinib ($P < .001$). At 12 months, 231 patients (29.8%) achieved a DMR: 85 (22%) with imatinib, 55 (40%) with dasatinib and 91 (38%) with nilotinib ($P < .001$, Table 2). When considering the whole cohort of 1777 patients, achieving at least ≥MR2 at 3 months was predictive of a DMR at any timepoint of observation with any frontline TKI: with imatinib 67% versus 30% of patients with <MR2, with dasatinib 66% versus 28% of patients with <MR2 and similar results have been reported with nilotinib 75% versus 30% of patients with < MR2 at 3 months ($P < .001$). At the same time points (Table 3), as already reported, achieving at least ≥MR3 is even more predictive of a DMR at any timepoint: 89% versus 38% of patients with <MR3 with imatinib ($P < .001$), 84% versus 40% of patients with <MR3 with dasatinib ($P < .001$), and 89% versus 49% of patients with <MR3 with nilotinib ($P < .001$, Table 3).

Out of 1777 patients analyzed, 908 reached a DMR; 461 (51%) of them lost the response: the loss of response after >2 years was significantly higher in patients who at 3 months had ≥MR2 (18% vs. 9.9% of pts with <MR2, $P = .038$).

No differences among the 3 TKIs were revealed in patients who maintained a DMR and were considered eligible for TFR: 106 (27%) with imatinib, 49 (26%) with dasatinib, and 105 (32%) with nilotinib (Table 4).

According to several studies, TFR is associated with increased outcome only in patients who maintained a long-term treatment (more than 5 years) and a sustained DMR. The correlation with long-term treatment was showed in the first French STIM study,[14] in which a reduced risk of molecular relapse was recorded in patients with a long exposure to imatinib for more than 54 months and in the EUROSKI study[15] that identified a low risk in patients exposed to TKIs for more than 5.8 years. A similar correlation was also reported with second-generation TKIs, a similar correlation was reported: in the ENESTfreedom trial,[16] a prolonged therapy with nilotinib was associated with a higher rate of sustained TFR. Similarly, also for the long duration of DMR: both the EUROSKI and the mentioned ENESTFreedom studies showed a reduced relapse rate associated with a long duration of MR4 or MR4.5.[15,16] In our study, analyzing a large cohort of centralized samples in standardized laboratories, we found a correlation between faster responses at early time points and an increased rate of DMR. Moreover, as already reported, the use of second-generation TKIs

Table 3 Predictive Value of MR3 at 3 Months on the Achievement of DMR

	Imatinib				Dasatinib				Nilotinib			
	Overall No = 909	MR < 4 No = 510	MR ≥ 4 No = 399	*P*-Value	Overall No = 351	MR < 4 No = 166	MR ≥ 4 No = 185	*P*-Value	Overall No = 517	MR < 4 No = 193	MR ≥ 4 No = 324	*P*-Value
MR (3 mo)				<.001				<.001				<.001
MR < 3	798 (100%)	498 (62%)	300 (38%)		252 (100%)	150 (60%)	102 (40%)		340 (100%)	174 (51%)	166 (49%)	
MR ≥ 3	111 (100%)	12 (11%)	99 (89%)		99 (100%)	16 (16%)	83 (84%)		177 (100%)	19 (11%)	158 (89%)	

Table 4 TFR Eligibility

	Overall, No = 908	Imatinib, No = 399	Dasatinib, No = 185	Nilotinib, No = 324
Treatment free, N (%)				
Eligible	260 (29%)	106 (27%)	49 (26%)	105 (32%)
Not eligible	388 (43%)	178 (45%)	81 (44%)	129 (40%)
Too early	260 (29%)	115 (29%)	55 (30%)	90 (28%)

improved over time the rate of DMR and the possible eligibility to discontinuation. The loss of response during treatment seems also correlated with the time to response, significantly increased for patients who at 3 months had ≥MR2. As compared to previous reports, there is a strong correlation between the deepness of molecular response and the rate of DMR achieved at last observation; nevertheless, in our analysis achieving at least ≥ MR2 at 3 months is equally significant in terms of DMR rate, regardless of type of drug used. Branford and colleagues analyzed the prognostic factors that influenced the incidence of sustained MR4.5 (strictly to undetectable for > 2 years) in a large cohort of CML patients treated with imatinib. The results showed that female sex, for unknown reasons, and the *BCR::ABL1* value at 3 months were the independent predictors of stable DMR; in particular, the highest incidence of MR4.5 at 8-years was 78% for patients with < 0.10% at 3 months compared to 52.7% of patients with a ratio >0.10%-1% and 29% for patients with >1%-10%.[17]

The German group reported that the 3-month *BCR::ABL1* transcript value identifies patients at risk of impaired OS: roughly half-log reduction from the baseline value and a 6% IS value (extrapolated from BCR-ABL/GUS analysis) at 3 months were associated with low OS.[7]

Recently, the same group analyzed 510 patients after a median follow-up of 5.4 years. Most of the patients were treated with second generation TKIs (59%): milestones according to ELN criteria were achieved by 88%, 85%, and 73% of patients at 3,6, and 12 months, respectively. A DMR was achieved by 85%, 86%, and 91% of patients who reached the milestones at 3, 6, and 12 months, respectively, compared to 44%, 45%, and 51% of patients who did not. A TFR eligibility was achieved prevalently with nilotinib (32%) compared to imatinib (14%) and dasatinib (13%), with only 19% of patients who discontinued.[18]

In a large cohort of CML patients analyzed in a standardized network of laboratories we report that, regardless the type of drug used, reaching at least ≥MR2 and a MR3 at 3 months it seems predictive of a DMR at any time point. Considering the prerequisite for a discontinuation a sustained DMR, only a minority of patients can be eligible for the discontinuation, regardless the frontline treatment received. These results suggest that in order to improve the rate of TFR, new treatment options or investigational approaches should be applied.

Author Contributions

AP, RC, GM, MM extrapolated the data and made the analyses; MB wrote the manuscript; FC, SG, BI, FS, SS, MB, DC, AI, GM, GR, FS enrolled patients, PF, MV, and FP revised the paper.

CRediT authorship contribution statement

Massimo Breccia: Writing – review & editing, Writing – original draft, Conceptualization. **Rosalba Cucci:** Data curation, Conceptualization. **Giovanni Marsili:** Project administration, Data curation. **Fausto Castagnetti:** Validation, Investigation. **Sara Galimberti:** Investigation, Data curation. **Barbara Izzo:** Validation, Resources, Methodology. **Federica Sorà:** Validation, Investigation, Data curation. **Simona Soverini:** Validation, Methodology, Investigation. **Monica Messina:** Validation, Formal analysis, Data curation. **Alfonso Piciocchi:** Methodology, Investigation, Formal analysis, Data curation. **Massimiliano Bonifacio:** Validation, Investigation. **Daniela Cilloni:** Validation, Methodology, Investigation. **Alessandra Iurlo:** Validation, Investigation. **Giovanni Martinelli:** Validation, Methodology, Investigation. **Gianantonio Rosti:** Validation, Methodology, Investigation. **Fabio Stagno:** Validation, Methodology, Investigation. **Paola Fazi:** Visualization, Funding acquisition, Data curation. **Marco Vignetti:** Visualization, Project administration, Funding acquisition. **Fabrizio Pane:** Writing – review & editing, Validation, Investigation, Conceptualization.

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References

1. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34(4):966–984.
2. Hugues TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alpha plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2003;349(15):1423–1432.
3. Branford S, Rudzki Z, Harper A, et al. Imatinib produces significantly superior molecular responses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. *Leukemia*. 2003;17(12):2401–2409.
4. Hughes TP, Hochhaus A, Branford S, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). *Blood*. 2010;116(19):3758–3765.
5. Hanfstein B, Muller MC, Hehlmann R, et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). *Leukemia*. 2012;26(9):2096–2102.
6. Marin D, Ibrahim AR, Lucas C, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *J Clin Oncol*. 2012;3(3):232–238.
7. Hanfstein B, Shlyakhto V, Lauseker M, et al. Velocity of early BCR-ABL transcript elimination as an optimized predictor of outcome in chronic myeloid leukemia (CML) patients in chronic phase on treatment with imatinib. *Leukemia*. 2014;28(10):1988–1992.
8. Branford S. Why is it critical to achieve a deep molecular response in chronic myeloid leukemia? *Haematologica*. 2020;105(12):2730–2737.
9. Branford S, Yeung DT, Parker WT, et al. Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline. *Blood*. 2014;124(4):511–518.

10. Branford S, Kim D-W, Soverini S, et al. Initial molecular response at 3 months may predict both response and event-free survival at 24 months in imatinib-resistant or -intolerant patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase treated with nilotinib. *J Clin Oncol*. 2012;30(35):4323–4329.
11. Jain P, Kantarjian H, Nazha A, et al. Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: results with four tyrosine kinase inhibitor modalities. *Blood*. 2013;121(24):4867–4874.
12. Claudiani S, Gatenby A, Szydlo R, et al. MR4 sustained for 12 months is associated with stable deep molecular responses in chronic myeloid leukemia. *Haematologica*. 2019;104(11):2206–2214.
13. Kantarjian H, Branford S, Breccia M, et al. Are there new relevant therapeutic endpoints in the modern era of the BCR::ABL1 tyrosine kinase inhibitors in chronic myeloid leukemia? *Leukemia*. 2024;38(5):947–950.
14. Mahon FX, Rea D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for a least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*. 2010;11(11):1029–1035.
15. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19(6):747–757.
16. Hochhaus A, Masszi T, Giles FJ, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. *Leukemia*. 2017;31(7):1525–1531.
17. Branford S, Yeung DT, Parker WT, et al. Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline. *Blood*. 2014;124(4):511–518.
18. Kohlbrenner K, Galuschek N, Fabarius A, et al. European Leukemia Net milestones and their prognostic relevance for achieving deep molecular response and treatment-free remission in routine care: results of the German CML Registry. *Hemasphere*. 2024;8(s1):P713.